Current Concepts in Management of Stage I NSGCT

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Abstract While about 50% of non- seminomatous germ cell tumors of the testes present as clinical stage I (CSI), further management of these patients continues to be mired in controversy. Active surveillance is a frontline option for low- risk CS I patients and according to some, even the high- risk ones with high embryonal carcinoma (ECA) component and vascular invasion (VI). However, it carries the disadvantage of long- term surveillance, the need for prolonged chemotherapy in case of recurrence and the possibility of secondary malignancies due to radiation exposure from frequent CT scans. One or two cycles of BEP chemotherapy is a popular alternative to active surveillance which carries a very low relapse rate, but valid concerns about overtreatment of a majority of patients, with the attendant chemotherapy- related toxicity exist. Retroperitoneal lymph node dissection has been used as a means of avoiding chemotherapy, especially in high- risk patients, but carries the disadvantage of a high surgical morbidity and complications. As with any major surgical procedure, the best results are dependent on the experience and skill of the individual surgeon.

Keywords Testicular cancer · Non seminomatous germ cell tumor · Stage I NSGCT · Retroperitoneal lymph node dissection · Active surveillance · BEP chemotherapy

Introduction

Approximately 50% of patients with non-seminomatous germ cell testicular cancers (NSGCT) are classified as clinical stage I disease (CS1). The standard treatment options of patients with clinical stage I disease include retroperitoneal lymph node dissection (RPLND), active surveillance or primary chemotherapy. The controversy however remains over the choice of modality since patients have an excellent survival with all the modalities with cancer-specific survival rates of 98 to 99%. Furthermore, from large surveillance series, we know that 25 to 30% of patients diagnosed with CS1 disease ultimately will relapse due to occult microscopic retroperitoneal lymph node metastases, which cannot be reliably detected by modern imaging studies, tumour markers or molecular approaches [1–3]. The risks and benefits of treatment modalities differ [4]. The current challenge in the management of CS1 NSGCT is to achieve a cure, with minimal treatment-related acute or long-term toxicity.

NSGCT CS1: Definition and Staging

Clinical stage I is defined by negative imaging studies of the chest, abdomen and pelvis. Furthermore, in order to verify clinical stage I disease, elevated markers should be followed post-orchidectomy until normalization. Patients without marker normalization or those in whom markers do not decline according to their half-life after orchidectomy do not have stage I disease.

Recommendations concerning staging investigations are frequently based on low-level evidence rather than on the results of prospective phase III studies. Computerized tomography (CT) of the chest, abdomen and pelvis are required as initial staging investigations with the mandatory application of oral and intravenous contrast media [5, 6]. For the evaluation of the lung and mediastinum, chest CT scan is more sensitive than plain X-ray films [7, 8]. However, pulmonary/pleural

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nodules of <1 cm can represent a false positive finding in CT scans [8]. Furthermore, CT scans of the abdomen and pelvis might give false-negative results in up to 30% of cases due to difficulties in the interpretation of lymph nodes based on morphology and size alone [5]. Therefore, the differentiation between clinical stages I and IIA might be unreliable. Magnetic resonance tomography (MRT) scans of the abdomen and pelvis do not provide additional information and should be restricted to patients to whom intravenous contrast media cannot be given [9]. Based on available data, positron emission tomography (PET) has not conclusively demonstrated to improve sensitivity over staging by doing CT scanning alone [10, 11]. PET scans are not recommended as a part of routine initial staging procedures outside clinical trials.

Prognostic Risk Factors

Several studies have reported on the prognostic factors for occult metastatic disease in CS1 NSGCT. Presence of embryonal cell carcinoma, absence of endodermal sinus tumour and invasion of tumour cells into blood and lymphatic vessels have been found to be predictors of relapse [1, 12, 13]. Subsequent studies have shown that vascular invasion (VI) is the single most important prognostic factor regarding risk of relapse [14–17]. Without adjuvant treatment, the high-risk group (VI positive) has a 3-year relapse rate of approximately 50%, while low-risk patients (VI negative) have a relapse risk of 10 to 20% [1, 3, 16–22].

Risk-adapted approach based on VI alone results in an unnecessary overtreatment rate of about 50%. Hence, prognostic indicators including proliferation rate as well as the percentage of embryonal carcinoma in relation to the total tumour volume are also considered [23, 24]. The combination of absence of VI and a percentage of embryonal carcinoma <45% correctly identified 91.5% of all patients with true pathological stage I disease [23]. On the other hand, the presence of VI and a percentage of embryonal carcinoma >80% correctly predicted pathological stage IIA/B disease in 88% of the patients. Based on these data, the German Testicular Cancer Study Group performed a prospective study in which 200 patients with clinical stage I NSGCT were assigned to RPLND and risk factors were assessed prospectively [24]. The combination of absence of VI, percentage of embryonal carcinoma <50% and a MIB-1 proliferating index <20% had negative predictive value of 86.5% for pathological stage II disease.

NSGCT Clinical Stage I: Management Options

Up to 30% of NSGCT patients with clinical stage I (CS1) disease have subclinical metastases and will relapse if surveillance alone is applied after orchiectomy. The decision regarding adjuvant treatment should always be based on a thorough discussion with the patient, taking into account the described advantages and disadvantages, as well as the individual situation of the patient.

Active Surveillance

Active surveillance represents a treatment strategy with the aim to detect retroperitoneal or systemic relapses and to treat only patients with documented metastatic disease thereby decreasing the risk of unnecessary overtreatment. Improvements in clinical staging and follow-up methods, and the availability of effective salvage treatment with cisplatin-based chemotherapy and post-chemotherapy surgery, have led to studies and establishment of close surveillance after orchiectomy as a standard treatment option in low-risk CS1 NSGCT patients.

When recommending active surveillance for low risk or in certain scenarios also for stage I high-risk NSGCT, two major important aspects have to be considered: (1) risk of secondary malignancies due to the repetitive radiation exposure of the imaging studies and (2) more intensive treatment in case of relapse which includes three cycles of bleomycin, etoposide and cisplatin (BEP) $\pm$ post-chemotherapy RPLND as compared to primary active therapy (one cycle BEP).

The largest reports of the surveillance strategy indicate a cumulative relapse rate of about 30%, with 80% of relapses occurring during the first 12 months of follow-up, 12% during the second year and 6% during the third year, decreasing to 1% during the fourth and fifth years, and occasionally even later [1, 3, 12, 25]. About 35% of relapsing patients have normal levels of serum tumour markers at relapse. Despite very close follow-up, 11% of relapsing patients presented with large-volume recurrent disease.

Relapses occur in the retroperitoneum in 54–78% of patients, in the lung in 13–31%, but are very rarely found in more than one visceral organ. With this approach, 78–86% of patients do not need any further treatment after orchiectomy [1, 24–28]. If a patient under surveillance relapses, the administration of chemotherapy will result in a cure rate close to 100%. Only in circumstances not suitable for surveillance is adjuvant chemotherapy with two cycles of BEP recommended.

The European Germ Cell Cancer Consensus Group (EGCCCG) has recommended that for patients with a low risk of relapse (no. VI), surveillance should include at least five CT scans performed at 0, 3, 12, 18 and 24 months [29]. This follow-up protocol with extensive imaging studies, however, might lead to a high-radiation exposure with significant long-term consequences for the patients.

Tarin et al. [30] estimated the risk of secondary cancer associated with imaging-related radiation during surveillance of stage I NSGCT using computerized tomography (CT). In their analysis, they evaluated surveillance protocols recommending about 16 CT scans over a 5-year period, and they took into consideration a 64-slice CT scanner obtaining images of the abdomen and pelvis with and without the chest. With a 5-year surveillance protocol, the lifetime cancer risk ranged from 1 in 52 (1.9%) for an 18-year-old patient to 1 in

63 (1.2%) for a 40-year-old patient. If chest CTs were also obtained, the risk increases to 1 in 39 (2.6%) and 1 in 58 (1.6%), respectively. The relative risk of a secondary malignancy with surveillance compared to a single scan after RPLND is approximately 15.2.

Various studies have been designed to reduce the number of CT scans during the surveillance strategy [31, 32]. The prospective-randomized Medical Research Council Trial TE08 was initiated which compared the diagnostic efficacy of two versus five CT scans during the first 2 years of follow-up to detect the number of patients who have intermediate and poor prognosis disease at relapse [32]. Patients with clinical stage I NSGCT opting for surveillance were randomly assigned to chest and abdominal CT scans at either 3 and 12 or 3, 6, 9, 12, and 24 months, with all other investigations identical in the two arms. No patients had poor prognosis at relapse, but two (0.8%) of those relapsing in the two-scan arm had intermediate prognosis compared with 1 (0.6%) in the five-scan arm, a difference of 0.2% (90% CI, -1.2 to 1.6%). No deaths were reported. This large prospective-randomized trial concluded that CT scans at 3 and 12 months after orchiectomy should be considered a reasonable option in low-risk patients. It is however unclear if this approach of reduced imaging studies can be applied for high-risk patients since only 10% of the recruited NSGCT demonstrated vascular invasion with a relapse rate of 32%.

Risk-Adapted Treatment Risk-adapted treatment is an alternative to the strategy of surveillance for all patients with CS1 NSGCT. Risk-adapted treatment is based on the risk factor, vascular invasion. Stratifying patients with CS1 NSGCT according to their presumed risk of relapse is a rational option, as several studies have reported similar survival rates and a final cure rate close to 100% with all available treatment options using the risk-stratifying approach [28, 33–43].

If the risk-adapted policy is applied, patients with vascular invasion are recommended to undergo adjuvant chemotherapy, and patients with absent vascular invasion are recommended a surveillance strategy. In the past, two cycles of BEP have been recommended for adjuvant treatment. In view of the low rates of recurrence (2–3%) and equivalent cancer-specific survival rates including salvage strategies in large prospective trials with sufficient follow-up, one cycle of BEP is recommended as adjuvant chemotherapy in patients with vascular invasion. In cases of relapse after BEP $\times 1$, three courses of BEP are recommended. However, there is not a large body of evidence to support one specific salvage regimen.

A risk-adapted strategy based on the presence of VI with the application of 2 cycles PEB chemotherapy is the recommended standard procedure according to the EGCCCG and the European Association of Urology (EAU) guidelines, although an overtreatment rate of 52% results due to this fairly insensitive marker [29].

Non-Risk-Adapted Approach Non-risk-adapted approach for surveillance in CS1 NSGCT has been studied. In a retrospective study, all patients with CS1 NSGCT referred from 1998 to 2007 to the British Columbia Cancer Agency and the Oregon Testis Cancer Program were reviewed [44]. A total of 233 patients was identified, of which 223 chose active surveillance. Vascular invasion (VI) was absent, present and unknown in 66, 27 and 7% of cases, respectively. Overall, 49% of patients had embryonal predominant disease. Fifty-nine patients (26%) relapsed, all but one with good prognosis disease. VI was present in only half (30/59) of the relapsed patients. Most patients relapsed within 2 years (88%), and only 7 of 223 patients (3%) relapsed beyond 2 years. All relapses were in long-term remission following chemotherapy with or without RPLND. Only 17 of 223 patients (8%) required post-orchietomy surgery. Disease-specific survival was 100% after a median follow-up of 52 months (3–136 months), and none of the patients required second-line chemotherapy. This study advocated active surveillance for all CS1 NSGCT patients with excellent outcomes comparable with the best results reported with primary RPLND or adjuvant chemotherapy. Nearly 75% of patients are spared any therapy after orchiectomy.

Kakiashvili et al. reported on the largest experience of non-risk-adapted surveillance in 371 patients with clinical stage I NSGCT [45]. From 1981 to 2005, 371 patients with CS1 NSGCT were placed on an active surveillance protocol. Recurrence patterns, predictors of relapse and disease-specific (DS) and overall survival (OS) were measured. Outcomes were stratified into two cohorts by their time of diagnosis (initial, 157 patients (1981–1992); recent, 214 patients (1993–2005)). Median follow-up was 6.3 years, and median time to relapse was 7.1 months. Lymphovascular invasion ($P < 0.0001$) and pure embryonal carcinoma ($P = 0.02$) were independent predictors of relapse. In the initial cohort, 66/157 (42.0%) were high risk and 36/66 (54.5%) relapsed versus 17/91 (18.7%) low risk ($P < 0.0001$). In the recent cohort, 59/214 (27.6%) patients were high risk and 29/59 (49.2%) recurred versus 22/155 (14.2%) low risk ($P < 0.0001$). The 5-year disease-specific survival (DSS) and overall survival (OS) were 99.2 and 98.2%, respectively. They concluded that non-risk-adapted active surveillance for all CS1 NSGCT patients including those at high risk, provided nearly 100% cure rate with reduced overall treatment burden. Approximately half of the high-risk patients will be spared unnecessary treatment with little or no increase risk by this approach.

Furthermore, studies have questioned the high recurrence rate of close to 50% and reported it to be 30–35% [19, 32, 46]. Based on these findings, some authors offered surveillance even to patients with high-risk CS1 NSGCT with excellent outcomes [44, 45].

Based on the results presented, active surveillance might be used in both low- and high-risk clinical stage

I NSGCTs. Whereas it represents the standard approach in low-risk patients with an expected relapse rate of 12–15%, high-risk patients and physicians who follow the surveillance strategy have to be informed about the 50% relapse risk and the urgent need to adhere to strict follow-up schedules in order to maintain the high cure rate.

Chemotherapy

Preferred Regimen In the past, patients with a high risk of relapse (VI present) were recommended adjuvant chemotherapy with two cycles of BEP [29, 47]. Minimizing toxicity is important in all adjuvant chemotherapy (ACT) studies. Accordingly, trials have evaluated alternatives to BEP.

The Swedish and Norwegian Testicular Cancer Group (SWENOTECA) study group evaluated the alternate regimen and reported the long-term results of follow-up after risk-adapted treatment in clinical stage I NSGCT implementing adjuvant CVB chemotherapy. They concluded that application of cytotoxic regimes such as cisplatin, vinblastine and bleomycin was associated with an unacceptable high frequency of treatment-related toxicities and does not play any role in the adjuvant management of clinical stage I NSGCTs [43].

The substitution of BOP for BEP chemotherapy, in which etoposide was replaced by vincristine, resulted in no gain in toxicity, although efficacy was retained [48]. Similarly, replacing cisplatin with carboplatin has been discarded since, despite optimistic conclusions, the occurrence of two deaths from chemotherapy-resistant disease in 52 cases casts doubt upon the safety of this approach [49]. The inferior results of carboplatin versus cisplatin in good prognosis metastatic NSGCT have reinforced concerns over this substitution as an adjuvant therapy, and BEP remains the preferred choice [50].

The disadvantage of adjuvant treatment in high-risk patients is that half of the patients who receive adjuvant BEP would not have required chemotherapy at all and may be unnecessarily exposed to the side effects of chemotherapy [51–55], a possible transient decrease in fertility [56] and possibly a small risk of secondary malignancies, as reported from patients receiving higher doses of chemotherapy [57].

BEP (One Vs Two Cycles) Following the failure of drug substitutions to convincingly reduce the toxicity of ACT, the next step was clearly to examine a single cycle of full dose (etoposide total dose 500 mg/sqM) BEP [58–62]. Very encouraging results were reported in the following two European studies:

The Swedish and Norwegian TC Project (SWENOTECA)

SWENOTECA had previously evaluated risk-adapted treatment in CS1 NSGCT [39]. From 1998 to 2005, 745 Norwegian and Swedish patients were included into a prospective, community-based multicenter SWENOTECA management program. Treatment strategy depended on the presence or absence of vascular tumour invasion (VI). VI positive patients were recommended brief (one or two cycles) adjuvant chemotherapy with BEP, whereas VI negative patients could choose between one cycle of ACT and surveillance. They concluded that at a median follow-up of 4.5 years, one course of adjuvant BEP reduces the risk of relapse by approximately 90% in both VI positive and VI negative CS1 NSGCT and may be a new option as initial treatment for all CS1 NSGCT. One course of adjuvant BEP for VI positive clinical stage I reduces the total burden of chemotherapy compared with surveillance or two courses of BEP.

The updated and expanded results from SWENOTECA group confirm a low relapse rate following one course of adjuvant BEP in CS1 non-seminoma [40]. At a median follow-up of 7.9 years, 12 relapses had occurred, all with the International Germ Cell Cancer Collaborative Group (IGCCCG) good prognosis. The latest relapse occurred 3.3 years after adjuvant treatment. The relapse rate at 5 years was 3.2% for patients with LVI and 1.6% for patients without LVI. Five-year cause-specific survival was 100%. The updated and expanded results confirmed a low-relapse rate following one course of adjuvant BEP in CS1 non-seminoma. SWENOTECA currently recommends one course of BEP as a standard treatment of VI positive CS1 NSGCT, whereas both surveillance and one course of BEP are options for VI negative CS1 NSGCT.

German TC Study AH 01/94

In a prospective-randomized clinical phase III trial, the German Testicular Cancer Study Group (GTCSG) randomized 382 patients with CS1 NSGCT to either receive 1 cycle of BEP chemotherapy or RPLND [43]. After a median follow-up of 4.7 years, 2 (1.04%) and 15 (7.8%) recurrences were detected in the chemotherapy and in the RPLND arm, respectively, resulting in a 2-year recurrence-free survival rate of 99.46% versus 91.87% ($P = 0.001$). The hazard ratio to experience a cancer recurrence with RPLND as opposed to chemotherapy was 7.937. Although RPLND was associated with a significantly higher relapse rate, it should be considered that RPLND was performed in numerous centres with variable surgical experience which might have contributed to the relatively high frequency of intra-abdominal relapses as compared to other studies.

Ongoing Trial: the UK National Cancer Research Institute TC Clinical Study Group

The UK National Cancer Research Institute TC clinical study group is conducting a single-arm study of one cycle of adjuvant BEP chemotherapy in high-risk (VI+) stage I NSGCTT (111 trial). It is a multicentre study to evaluate whether one cycle of adjuvant bleomycin, etoposide and cisplatin (BEP) chemotherapy results in a 2-year recurrence rate of less than 5% in patients with high-risk, stage I non-seminomatous germ cell tumours of the testis (NSGCTT). Two hundred forty-six patients with histologically proven NSGCTT or mixed germ cell tumours with vascular invasion and stage I disease within 6 weeks of having orchidectomy were recruited from 33 UK sites over 4.5 years. Patients received a single cycle of adjuvant BEP chemotherapy and are being followed up annually following completion of treatment.

Retroperitoneal Lymph Node Dissection

According to the EGCCCG and the EAU guidelines, in patients unwilling to undergo a surveillance strategy or adjuvant chemotherapy, nerve-sparing lymphadenectomy (NS-RPLND) may be performed [29, 47, 62].

The retroperitoneum is the usual site of relapse in more than 80% of patients with CS1 NSGCT [63]. RPLND provides accurate staging information regarding retroperitoneal (RP) lymph node status. Virtually all patients who relapse after primary RPLND are chemotherapy naïve and eventually cured by usually 3 cycles of cisplatin-based chemotherapy. Only a minority of CS1 NSGCT harbours occult systemic metastatic disease and might be better managed by inductive systemic chemotherapy.

RPLND simplifies follow-up and makes it more liberal. Subsequent RP relapse is rare, and abdominal imaging can be restricted to one baseline CT a few months after surgery. With the introduction of nerve-sparing technique along with various modified templates, antegrade ejaculation rates of 90–100% have been reported, with significantly reduced morbidity and virtually unknown mortality [64–66]. It is important to be aware of slow-growing retroperitoneal teratomas after primary chemotherapy [67]. Retroperitoneum is the most frequently involved site of chemoresistant mature teratoma which holds the potential of malignant transformation and late relapse if left unresected [68, 69].

Opponents of nerve-sparing RPLND argue that up to 75% of patients with CS1 NSGCT managed by primary RPLND will undergo unnecessary treatment. However, this only holds true if a non-risk-adapted strategy is chosen in every single CS1 patient. In view of the high cancer-specific survival rates of surveillance with salvage treatment in cases of relapse and the low relapse rates if adjuvant chemotherapy is chosen, the role of primary diagnostic retroperitoneal lymph node dissection has diminished.

The randomized phase III trial of the German Testicular Cancer Study Group compared RPLND to BEP $\times 1$ as adjuvant treatment to show a more than expected difference of 7% in favour of chemotherapy. One course of BEP showed a significantly lower recurrence rate as compared to surgery [61]. If RPLND is performed in a multicentre setting, a higher rate of “in-field” recurrences and complications was reported [61, 70]. Thus, nerve-sparing RPLND—if indicated—should be performed by an experienced surgeon in specialized centres.

Patient selection factors on outcome after primary RPLND have been reported, and the application of these parameters might allow a risk-adapted indication RPLND [63]. The question, however, remains if patients with embryonal carcinoma (ECA) predominance and/or vascular invasion (VI) should undergo RPLND or primary chemotherapy due to an anticipated high risk of systemic relapse following locoregional surgical treatment.

Stephenson et al. analysed the outcome of 267 patients with CS1 and CS IIA NSGCTs with one or two of the aforementioned risk factors who underwent nerve-sparing RPLND [46]. ECA and VI were present in 31% of the patients and ECA without VI was identified in 10%, whereas 58% demonstrated VI without ECA. One hundred twenty-nine (66%) patients with CS1 and 26 (37%) with CS IIA had pathological stage I disease. One hundred twelve patients demonstrated lymph node metastases, and 60 (54%) and 52 (46%) demonstrated pN1 and pN2 disease, respectively. The presence of both risk factors was associated with a significantly higher risk of retroperitoneal metastases (54 versus 37%, $P = 0.009$); however, the risk to harbour pN2 disease was not significantly increased. Patients with pathological stage I were followed actively and did not receive adjuvant chemotherapy, whereas 22 and 83% of patients with pN1 and pN2 disease received adjuvant cytotoxic treatment with 2 cycles, respectively. All patients remained disease free during the complete follow-up period. Sixteen percent of pathological stage II patients had teratoma in the retroperitoneum, which would not have been eliminated by primary chemotherapy. Two hundred eleven patients did not receive adjuvant chemotherapy, and 26 (12.3%) patients experienced relapse with four recurrences developing in the retroperitoneum due to a modified template resection. The 5-year progression-free survival probability including a full bilateral template would be 90%. All relapsing patients could be salvaged by 4 cycles of EP chemotherapy. Summarizing the data of the total cohort of 267 patients, 80 (29.9%) CS1/IIA high-risk patients received either adjuvant or salvage chemotherapy. If only high-risk CS1 NSGCT are considered an estimated 89% would have been free of progression 5 years after chemotherapy.

Rassweiler et al. assessed the role of laparoscopic RPLND in the management of CS1 NSGCT reviewing the literature comprising a total of more than 800 patients [71]. Whereas no significant differences with regard to complications could be

observed when compared to open RPLND, it became evident that more than 90% of patients with positive lymph nodes underwent adjuvant chemotherapy making laparoscopic RPLND a mere staging surgery. However, the laparoscopic approach is feasible in highly specialized centres; the curative potential of this approach still has to be evaluated.

When discussing nerve-sparing RPLND as primary treatment option in patients with CS1 NSGCT, potential surgery-related complications have to be considered. Quite recently, the German Testicular Cancer Study Group evaluated the outcome of 239 CS1 NSGCT who underwent nerve-sparing RPLND [70]. Minor and major complications were observed in 14.2 and 5.4%, respectively. Antegrade ejaculation could be preserved in 93.3% of the patients, and the frequency of ejaculation correlated significantly with the experience of the surgeon. Fourteen (0.8%) patients developed relapses with the majority ($n = 11$) being located in the extraperitoneal areas.

In summary, nerve-sparing RPLND seems to cure about 85 to 90% of patients with high-risk CS1 NSGCT, whereas 70% of low risk NSGCT are over treated due to a true pathological stage I in these patients.

Conclusions

Although armchair calculations of the odds of cure and toxicity associated with the various treatment options can be performed, recommendations about the most optimal therapy in clinical stage I NSGCT remain controversial.

All the three available treatment options including active surveillance, primary chemotherapy and nerve-sparing RPLND have approximately the same high cure rate reaching up to 100% but with significantly different long-term complications. As demonstrated, active surveillance can be performed in low- and high-risk NSGCT with an anticipated relapse rate of about 15 and 50%. Patients who experience relapse usually have good and intermediate prognosis tumours, which have to be treated with 3 to 4 cycles of chemotherapy. About 25 to 30% of these patients will have to undergo post-chemotherapy RPLND for residual masses. Primary chemotherapy with 1–2 cycles BEP is a therapeutic option for high-risk clinical stage I NSGCT associated with a recurrence rate of only 2–3% and a minimal acute and long-term toxicity rate. Nerve-sparing RPLND, if performed properly, will cure about 85% of all high-risk patients with clinical stage I NSGCT without the need for chemotherapy.

The treatment of CS1 disease should be patient-driven; apart from risk grouping as even in the ‘high-risk group’, only 50% harbour micrometastatic disease and the remaining 50% are cured with orchidectomy alone. While active surveillance seems to be the treatment strategy of choice for CS1 low-risk patients, the optimal management strategy for high-risk patients is still a matter of debate.

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